CLAIMS

What is claimed is:

1. A transgenic animal having somatic and/or germ cells comprising a nucleic acid which comprises a promoter region capable of directing protein expression in animal and/or human cells that is operably linked to a sequence comprising at least 15 contiguous nucleotides of SEQ ID NO: 2 including at least the thymine at position 582 of SEQ ID NO: 2.

2. A transgenic animal having somatic and/or germ cells comprising a nucleic acid which comprises a sequence which encodes SEQ ID NO: 4 and which includes at least a codon for the valine corresponding to the valine at position 171 of SEQ ID NO: 4, and wherein the nucleic acid further comprises an operably linked promoter region capable of directing protein expression in animal and/or human cells.

3. The transgenic animal of claim 1, wherein the nucleic acid comprises SEQ ID NO: 2.

4. A transgenic animal for the study of bone density modulation having somatic and/or germ cells comprising a nucleic acid which comprises a promoter region that directs protein expression in animal and/or human cells operably linked to a sequence comprising at least 15 contiguous nucleotides of SEQ ID NO: 1, wherein bone mass is modulated relative to non-transgenic animals of the same species in more than one parameter selected from among bone density, bone strength, trabecular number, bone size, and bone tissue connectivity.

5. The transgenic animal of claim 1, wherein the promoter region is a bone specific promoter region.

6. The transgenic animal of claim 4, wherein the promoter region is a bone specific promoter region.

7. The transgenic animal of claim 1, wherein the promoter region is a CMVβActin promoter region.

8. The transgenic animal of claim 1, wherein the promoter region is a type I collagen promoter region.

9. The transgenic animal of claim 1, wherein the transgenic animal express a human HBM protein.

10. The transgenic animal of claim 1, wherein the animal exhibits a HBM phenotype.

11. The transgenic animal of claim 10, wherein bone mass is modulated relative to a non-transgenic animal of the same species in more than one parameter selected from among bone density, bone strength, trabecular number, bone size, and bone tissue connectivity.

12. The transgenic animal of claim 1, wherein a human HBM protein is expressed and wherein the transgenic animal is fertile and passes the human *HBM* gene to its offspring.

13. The transgenic animal of claim 4, wherein a human LRP5 protein is expressed and wherein the transgenic animal is fertile and passes the human *LRP5* gene to its offspring.

14. A transgenic mouse having a genome comprising an alteration of the gene encoding LRP5 wherein the alteration is caused by the introduction of a nucleic acid for gene targeting by homologous recombination into embryonic stem cells or pluripotent cells comprising a first section homologous to mouse *LRP5* gene and a second section homologous to another section of mouse *LRP5* gene, and between the first and the second section a middle section comprising an engineered deletion of a portion of the *LRP5* gene, a nucleic acid sequence change, or a nucleic acid insertion, and wherein the nucleic acid is capable of homologous recombination with the endogenous gene.

15. The transgenic mouse of claim 14, wherein the middle section of the nucleic acid for gene targeting comprises an engineered deletion of the ATG start codon, an engineered frame-shift mutation, an engineered stop codon, a neomycin resistance sequence, a loxP recombination site, or a synthetic transcriptional pause sequence.

16. The transgenic mouse of claim 14, wherein the nucleic acid for gene targeting further comprises both intron and exon sequences of the mouse *LRP5* gene.

17. The transgenic mouse of claim 14, wherein the nucleic acid for gene targeting further comprises a codon encoding a glycine to valine change at position 170 of the amino acid sequence of the mouse *LRP5* gene, and wherein the altered gene encodes a HBM protein.

18. The transgenic mouse of claim 14, wherein the alteration is a disruption of the *LRP5* gene such that it is not expressed.

19. A transgenic mouse having a genome comprising an alteration of the gene encoding *LRP6,* wherein the alteration is caused by the introduction into embryonic stem cells or pluripotent cells of a nucleic acid for gene targeting by homologous recombination comprising a first section homologous to mouse *LRP6* gene and a second section homologous to another section of mouse *LRP6* gene, and between the first and the second section a middle section comprising an engineered deletion of a portion of the *LRP6* gene, a nucleic acid sequence change, or a nucleic acid insertion, and wherein the nucleic acid is capable of homologous recombination with the endogenous gene wherein the transgenic animal has modulated Wnt activity, Dkk activity, lipid levels or bone mass.

20. The transgenic mouse of claim 19, wherein the alteration is a disruption of the *LRP6* gene such that it is not expressed.

21. A method for studying bone mass development comprising the steps of:

(a) providing a first group of animals selected from among
  (i) animals comprising a transgene for expressing LRP5, LRP6 or HBM,
  (ii) animals in which the native LRP5 or LRP6 gene has been modified to express HBM or another variant or to prevent or modulate the expression of LRP5 or LRP6, or
  (iii) animals in which expression of LRP5 or LRP6 is otherwise disrupted or modulated; and,

(b) measuring at least one parameter of bone development in the animals.

22. A method for studying modulators of bone mass comprising the steps of claim 21, and further comprising a step of administering a test compound to at least some of the animals prior to measuring at least one parameter of bone development in the animals.

23. A method for studying the effect of a procedure on bone mass comprising the steps of the method of claim 21, and further comprising a step of administering an experimental procedure to at least some of the animals prior to measuring at least one parameter of bone development in the animals.

24. The method of claim 22, wherein the test compound is administered by injection, orally, by suppositories, in an implant, or topically.

25. A method according to claim 23, wherein the experimental procedure is chosen from among an ovariectomy, restricted bone loading, and increased bone loading.

26. The method of claim 22, wherein the test compound comprises a hormone, a growth factor, a peptide, an RNA, a DNA, a mineral, a vitamin, a natural product, or a synthetic organic compound.

27. The method of claim 23, wherein the experimental procedure comprises a surgical procedure, a gene therapy procedure, a drug therapy procedure, a dietary regimen, or physical exercise.

28. A method according to claim 21, wherein a group of transgenic animals are expressing HBM and wherein bone mass density is modulated in the

transgenic animals that are expressing HBM and are administered the test compound.

29. A method according to claim 21, wherein a group of transgenic mice are expressing HBM and wherein bone mass density is increased in the transgenic mice that express HBM and are administered the test compound.

30. A method for studying an effect of HBM on bone disorders comprising the steps of:

(a) providing embryos of animals with a bone disorder phenotype;

(b) introducing the nucleic acid of claim 1 into a first group of the embryos;

(c) transferring the embryos to pseudopregnant mice; and

(d) measuring at least one parameter of development in the resultant mice.

31. A method for studying an effect of HBM on bone disorders comprising the steps of:

(a) providing embryos of animals with a bone disorder phenotype;

(b) introducing the nucleic acid of claim 4 into a first group of the embryos;

(c) transferring the embryos to pseudopregnant mice; and

(d) measuring at least one parameter of development in the resultant mice.

32. A method for identifying surrogate markers of bone formation/resorption comprising the steps of:

(a) providing a first group of animals selected from among

(i) animals comprising a transgene for expressing LRP5, LRP6 or HBM,

(ii) animals in which the native LRP5 or LRP6 gene has been modified to express HBM or another variant or to prevent or modulate the expression of LRP5 or LRP6, or

(iii) animals in which expression of LRP5 or LRP6 is otherwise disrupted or modulated;

(b) providing a group of control animals;

(c) measuring quantitatively a candidate surrogate marker in the animals; and,

(d) comparing the measurements of a group of transgenic animals to measurements of the group of control animals.

33. A method for studying effects of the HBM gene on cardiac disorders comprising the steps of:

(a) providing a first group of transgenic animals selected from among

(i) animals comprising a transgene for expressing LRP5, LRP6 or HBM,

(ii) animals in which the native LRP5 or LRP6 gene has been modified to express HBM or another variant or to prevent or modulate the expression of LRP5 or LRP6, or

(iii) animals in which expression of LRP5 or LRP6 is otherwise disrupted or modulated; and

(b) measuring at least one parameter of cardiac health in the first group of animals administered a test compound.

34. A method for studying effects of a test compound and the HBM gene on cardiac disorders comprising the steps of the method of claim 33, and further comprising a step of administering a test compound to at least some of the animals prior to measuring at least one parameter of cardiac health in the first group of animals administered a test compound;

and wherein the test compound comprises a hormone, a growth factor, a peptide, RNA, DNA, a mineral, a vitamin, a natural product, or a synthetic organic compound.

35. The method of claim 34, wherein the parameter of cardiac health is blood serum lipid concentration.

36. A method of screening of cardio-protective treatments for bone mass modulation effects comprising the method of claim 21, and further comprising the step of administering a cardio-protective treatment to a subgroup of the first group of animals.

37. A method for identification of genes associated with bone mass comprising the steps of:

(a) providing an animal model of bone development comprising a first group of animals selected from among
  (i) animals comprising a transgene for expressing LRP5, LRP6 or HBM,
  (ii) animals in which the native LRP5 or LRP6 gene has been modified to express HBM or another variant or to prevent or modulate the expression of LRP5 or LRP6, or
  (iii) animals in which expression of LRP5 or LRP6 is otherwise disrupted or modulated;
(b) providing a group of control animals;

(c) measuring a profile of gene expression in the animals; and,

(c) comparing the measurements of a the first group of animals to measurements of the control group of animals.

38. A nucleic acid for gene targeting by homologous recombination comprising a first section homologous to mouse *LRP5* gene and a second section homologous to another section of mouse *LRP5* gene, and between the first and the second section a middle section comprising an engineered deletion of a portion of the *LRP5* gene, a nucleic acid sequence change, or a nucleic acid insertion, and wherein the nucleic acid is capable of homologous recombination with the endogenous gene.

39. The nucleic acid of claim 38, wherein the middle section comprises an engineered deletion of the ATG start codon, an engineered frame-shift mutation, an engineered stop codon, a neomycin resistance sequence, a loxP recombination site, or a synthetic transcriptional pause sequence.

40. The nucleic acid of claim 38, further comprising both intron and exon sequences of the mouse *LRP5* gene.

41. The isolated nucleic acid of claim 38, further comprising a codon encoding a glycine to valine change at position 170 of the amino acid sequence of the mouse *LRP5* gene.

42. A method of producing a transgenic mouse whose genome comprises an alteration of the gene encoding LRP5, the method comprising:

(a) providing the nucleic acid of claim 38;

(b) introducing the nucleic acid into mouse embryonic stem cells;

(c) selecting those embryonic stem cells that comprise the nucleic acid;

(d) introducing an embryonic stem cells of step (c) into a mouse blastocyst;
(e) transferring the blastocyst of step (d) to a pseudopregnant mouse; and
(f) allowing the transferred blastocyst to develop into a mouse chimeric for the nucleic acid.

43. The method of claim 42, wherein the introduction of the embryonic stem cell is by microinjection.

44. The method of claim 43, further comprising:
(a) breeding the chimeric mouse to a wild-type mouse to obtain mice heterozygous for the alteration; and
(b) breeding the heterozygous mice to generate mice homozygous for the alteration.